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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,611	10/06/2000	Maria Galanis	674537-2002	3929

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EXAMINER
OUSPENSKI, ILIA I

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/623,611	GALANIS ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2004 and 25 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-9,12-21,28,34,35,38 and 41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-9,12-21,28,34,35,38 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892).
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Ilia Ouspenski, Group Art Unit 1644, Technology Center 1600.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/02/2004 has been entered.

3. Applicant's amendment, filed 12/02/2004, is acknowledged.

Claims 1, 3, 10 – 11, 22 – 27, 29 – 33, 36 – 37, and 39 – 40 have been cancelled.

Claims 2, 4 – 7, 9, 12 – 13, 15, 18, 20 – 21, 28, 34 – 35, 38, and 41 have been amended.

Claims 2, 4 – 9, 12 – 21, 28, 34 – 35, 38, and 41 are pending.

4. Applicant's Petition to Amend Inventorship, filed 12/02/2004, is acknowledged, and has been granted. Gregory Coia has been removed as an inventor of this application.

5. This Office Action will be in response to applicant's arguments, filed 12/02/2004.

The rejections of record can be found in the previous Office Action.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

It is noted that New Grounds of Rejection are set forth herein.

6. Claim rejections – 35 USC 112, second paragraph: Applicant's amendment has obviated the rejections of record.

7. Claims 2, 4 – 9, 12 – 21, 28, 34 – 35, 38, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 4 – 9, 12 – 21, 28, 34 – 35, 38, and 41 are indefinite in the recitation of "CDR loop structure or part thereof," because the recitation of "part thereof" is inconsistent with the dependent limitation in paragraph (i) of "CDR loop structure." Thus one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

8. Claim rejections – 35 USC 112, first paragraph: Applicant's amendments have obviated the rejections of record.

9. Claim rejection under **35 USC 102(b) over Peach et al.**:

Claims 2, 7 – 9, 12 – 13, 20 – 21, 28, 34 – 35, 38, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Peach et al. (of record; J. Exp. Med., 1994, 180: 2049 – 2058; see entire document).

Applicant's arguments have been fully considered but were not found convincing.

Applicant argues that the rejection is assumed to be overcome, since claim 1 has been cancelled the remaining claims have been amended to depend from claim 2, which was not included in the rejection.

This is not found persuasive, because claim 2, as presently amended, is anticipated by the teachings of Peach et al. Specifically, Peach et al. teach non-antibody ligands (CTLA-4 and CD28), in which the V-like domain has been modified or replaced such that the size of a CDR loop structure has been altered (see entire document, in particular, e.g. Figures 1 and 3). Peach et al. further teach these ligands exist as mixtures of monomers and dimmers (page 2052 right column lines 9 – 12). Thus the reference teachings anticipate the instant claimed invention.

The rejection of record is maintained for the reasons of record, as it applies to the amended claims.

The rejection of record is reiterated herein for Applicant's convenience.

Applicant's arguments, filed 2/3/03, and arguing that the instant claims contribute a contribution over the teachings of Peach et al. have been fully considered as they apply to the instant rejection but have not been found convincing for the reasons set forth below.

Applicant's arguments, filed 1/24/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant submit that the pending claims are novel over Peach et al. in that Peach et al. only relates to CTLA4 molecules which are fused to an immunoglobulin fragment.

Applicant argues that the prior art is based, in part, on the erroneous premise that appearance of monomers in the gel samples is related to solubility. Solubility according to the specification, solubility relates to lack of aggregation of monomers, as assessed by HPLC chromatography. Applicant argues that there is nothing in Peach et al. to suggest that monomers are more soluble than dimers nor to suggest that any of the mutant chimeric proteins behave differently with respect to aggregation. Applicant further argues that the constructs in Peach et al. are not soluble in the sense of the word as defined in the instant application, existing as discrete non-aggregate molecules in aqueous solution, in the absence of detergents or other solubilizing entities.

As pointed out previously, Peach et al. teach chimeric molecules in which complementarity determining regions (CDRs) of CD28 and CTLA4 have been exchanged (see entire document, especially Table 2). Both CTLA4 and CD28 are T cell surface proteins that are non-antibody ligands comprising at least one monomeric V-like domain. Peach et al. show in Figure 4 that chimeric proteins such as HS4, HS4A, HS7, HS8, HS10, HS11, HS12 and HS13 each exist in monomeric form. The dimeric form of each chimeric molecule is also a "multivalent reagent comprising two or more binding moieties".

Again, Peach et al. teach that the binding affinity of at least some of these chimeric proteins is altered for B7-1 compared to the parent molecules (e.g., page 2052-2053). In addition, the chimeric proteins of Peach et al. each are a "binding moiety" since they bind monoclonal antibodies to CD28 (e.g., page 2052, bridging paragraph).

Although Peach et al. is silent with respect to the effect of these changes in the CDR loop structures on solubility, Peach et al. also show in Figure 4 that chimeric proteins HS10, HS11, HS12 and HS13 each exist in monomeric form at a greater frequency than do either CD28 or CTLA4. Thus Figure 4 provides objective evidence that at least the chimeric proteins HS4, HS4-A, HS7, HS8, HS10, HS11, HS12 and HS13 have improved solubility when compared with the unmodified VLDs of CD28 and CTLA4.

With respect to applicant arguments that Peach et al. do not teach the reader to modify CDR structures within a monomeric V-like domain in order to increase the solubility of the domain, there is no requirement that the prior art appreciate the properties inherent to the product.

As pointed out previously, applicant has further argued that the binding domains taught by Peach et al. are fusion proteins, and suggests that the fused Ig constant domain is needed to achieve solubility.

The Examiner again acknowledges that the chimeric proteins are fusion proteins. However, the "comprising" language of the claims encompasses fusion proteins. Further it is noted that in Figure 4 all of the proteins, including the wildtype CD28 and CTLA4 proteins, are evaluated in fusion protein form. Thus the increase in the lower molecule weight band corresponding to monomer in the above noted constructs reflects an effect of the CDR loop modification.

Applicant has further questioned whether the lower molecular weight bands are in fact monomers, noting that the gel is of immunoprecipitated material, that the arrows marking the position of CD28Ig and CTLA4Ig monomers does not correspond to any of the lower molecular weight bands, and that Peach et al. do not describe these forms as "monomers", but rather only as "additional species".

The Examiner acknowledges that the gel of Figure 4 is of material immunoprecipitated prior to loading and that aggregates would be lost. However, the appearance of any monomer, particular relative to the level of dimer, must necessarily indicate that there was overall a shift in equilibrium towards the monomer form relative to the unmodified molecules shown in the left lanes. The Examiner further notes that the immunoprecipitation step results in both monomeric and a multivalent form (i.e., the dimeric chimeric proteins) immobilized on a solid support, as recited in claim 21.

10. Claim rejection under **35 USC 102(e) over Koide et al.**: Applicant's amendment has obviated the rejection of record.

11. Claim rejection under **35 USC 102(f)**: Applicant's declaration under 37 CFR 1.132, filed 12/02/2004, and Petition to Amend Inventorship, filed 12/02/2004, have obviated the rejection of record.

12. Claim rejections under **35 USC 103(a) over Koide in view of Bogden et al. and over Koide in view of Cai et al**.: Applicant's amendment has obviated the rejections of record.

13. Claims 2 and 13 – 14 are rejected under **35 U.S.C. 103(a) as being unpatentable over Peach et al.** (of record; J. Exp. Med., 1994, 180: 2049 – 2058; see entire document) **in view of Bogden** et al. (of record; US Patent No. 5,504,069; see entire document).

Peach et al. have been discusses supra, and teach monomeric non-antibody ligands (CTLA-4 and CD28), in which the V-like domain has been modified or replaced such that the size of a CDR loop structure has been altered (see entire document, in particular, e.g. Figures 1 and 3, and page 2052, right column lines 9 – 12).

Peach et al. do not teach replacement of a CDR loop with a binding determinant derived from somatostatin.

Bogden et al. have been discussed in the prior Office Action, and teach that somatostatin agonists were highly desirable for methods including the inhibition of trauma-induced tumor growth (see entire document). Bogden et al. teach that native somatostatin has a very short half-life in vivo because the peptide is rapidly inactivated by endo- and exopeptidases; thus agonists which maintain the function of somatostatin but remain active for longer periods were highly desirable (e.g., see column 4 at lines 35-67). Bogden et al. review that it was well known in the art at the time the invention

was made that the somatostatin peptide could be modified in multiple ways to provide new structures that preserved the function of binding somatostatin receptors (see e.g., columns 5-8).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Bogden et al. to those of Peach et al. to obtain a claimed modified VLD, wherein one or more of the CDR loop structures is replaced with a binding determinant derived from somatostatin.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, in order to provide an agonist of somatostatin function of sufficient stability and size such that it would not be readily cleaved by endo- or exopeptidases, and could therefore remain active longer in vivo than the unmodified somatostatin peptide.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success, in view of the teachings in the art with respect to the production of agonists using the somatostatin peptide sequence.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 2 and 15 – 17 are rejected under **35 U.S.C. 103(a) as being unpatentable over Peach et al.** (of record; J. Exp. Med., 1994, 180: 2049 – 2058; see entire document) **in view of Cai et al.** (of record; PNAS, 1996, 93: 6280 – 6285; see entire document).

Peach et al. have been discusses supra, and teach monomeric non-antibody ligands (CTLA-4 and CD28), in which the V-like domain has been modified or replaced such that the size of a CDR loop structure has been altered (see entire document, in particular, e.g. Figures 1 and 3, and page 2052, right column lines 9 – 12). Peach et al. further teach that some of the altered ligands have a higher avidity for their targets (see e.g. the Abstract).

Peach et al. do not teach replacement of CDR loop structures with CDR loop structures derived from the human anti-melanoma antibody V86.

Cai et al. have been discussed in the prior Office Action, and teach the human anti-melanoma antibody V86 (see entire document). Cai et al. teach that unlike most antibodies, the specificity of V86 is contained within the VH domain since a full VL domain is not expressed by V86 (e.g., summarized in Abstract). Cai et al. note the art-recognized applications of anti-melanoma antibodies as immunodiagnostic reagents (e.g., page 6280 introduction). Cai et al. teach the amino acid sequence of the V86 antibody (see Table 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Cai et al. to those of Peach et al. to obtain a claimed a claimed modified VLD, wherein one or more of the CDR loop structures is replaced with CDR loop structures derived from the human anti-melanoma antibody V86.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, because of the teachings of Peach et al. that the resulting ligands may have a higher avidity, and the teachings of Cai et al. that the specificity of V86 is contained within the VH domain, and the art-recognized applications of anti-melanoma antibodies as immunodiagnostic reagents.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 2, 4 – 6, and 18 – 19 are rejected under **35 U.S.C. 103(a) as being unpatentable over Peach et al.** (of record; J. Exp. Med., 1994, 180: 2049 – 2058; see entire document) **in view of Koide** (of record; US Pat. Pub. No. 2003/0134386; see entire document).

Peach et al. have been discusses supra, and teach monomeric non-antibody ligands (CTLA-4 and CD28), in which the V-like domain has been modified or replaced such that the size of a CDR loop structure has been altered (see entire document, in particular, e.g. Figures 1 and 3, and page 2052, right column lines 9 – 12). Peach et al. further teach that some of the altered ligands have a higher avidity for their targets (see e.g. the Abstract).

Peach et al. do not teach modified monomeric non-antibody ligands wherein the size of the CDR loop structure has been increased by at least nine amino acids, or modified monomeric non-antibody ligands linked to a radioisotope.

Koide has bee discusses in the prior Office action, and teaches modified monomeric V-like domains based on Fn3 scaffold (see entire document, in particular, e.g. claims 1 and 2). Koide et al. further teach that the ability to label these ligands with radioisotopes makes them "an ideal model system for NMR studies on protein-protein interactions" (paragraph 0135). Koide further teaches modified monomeric V-like ligands which vary from unmodified ligands by an insertion of from two to 25 amino acids (e.g. claim 5).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Koide to those of Peach et al. to obtain the claimed modified monomeric non-antibody ligands linked to a radioisotope, or those with increased CDR loop structures.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, and have a reasonable expectation of success, because of the teachings of Koide that it is possible and highly desirable to label modified monomeric non-antibody ligands with a radioisotope for NMR studies.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Conclusion: no claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644
March 16, 2005

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3/17/05